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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,105	03/07/2000	ZIVA MESSIKA	MESSIKA=2	9465

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BROWDY AND NEIMARK
624 9TH STREET NW
SUITE 300
WASHINGTON, DC 20001

EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 11/18/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/445,105

Applicant(s)

MESSIKA ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

1. This office action is in response to the amendment and remarks filed on 6/13/03 in Paper No: 17. Applicant has amended claims 1, 2 and 7. Claims 1-12 are pending.
2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.
3. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.
4. Applicant's arguments filed 6 June 2003 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 102, withdrawn.

5. The rejection of claims 1, 2, 4, 7 and 12 under 35 U.S.C. 102(b) as being anticipated by Korn et al. (1988) is withdrawn because Applicant has amended the claims to recite only TNF-alpha without a labeled detectable group.

Claim Rejections - 35 USC § 102, maintained

6. The rejection of claims 1, 2, 4, 7 and 12 under 35 U.S.C. 102(b) as being anticipated by Korn et al. (1988) is maintained. Applicant argues that claims are amended to add a proviso that the TNF-alpha is not labeled with a detectable group. This argument has been fully considered but is not deemed persuasive. Korn et al. describe the production of TNF-alpha with (page 354) and without the label (page 352). The authors teach the use of ³⁵S-cysteine to produce metabolically labeled TNF in CHO cells for the use in western blots etc (page 354). Korn et al. also describe the production of label free TNF to be used in cytotoxicity studies (page 352). In addition, the rejection of claims 1, 2, 4, 7 and

12 under 35 U.S.C. 102(b) as being anticipated by Korn et al. (1988) is maintained for reasons stated in Paper Nos: 8, 10 and 16.

Claim Rejections - 35 USC § 103, maintained

7. The rejection of claims 3, 5, 6 and 8-11 under 35 U.S.C. § 103(a) as being unpatentable over Korn (1988) in view of Allet (U.S. Patent No: 5,487,984) is maintained for reasons stated in Paper No: 16. Applicant argues that the inherency of glycosylation in CHO cell produced TNF-alpha is relevant only to anticipation rejections. This argument has been fully considered but is not deemed persuasive. The office did not argue that the claims as a whole were anticipated over the references. The position of the Office is that since the protein of the instant invention and the protein of Korn et al. are made in the same mammalian cells (CHO cells) both TNF-alpha proteins would be expected to be glycosylated. In addition, contrary to Applicants assertion that Korn et al. never produced substantially homogeneous glycosylated human TNF which is not metabolically labeled, as noted above in paragraph 6, Korn et al. did produce human TNF which was not metabolically labeled in CHO cells. In addition, Korn et al. also show by immunoprecipitation a 17 KD protein from transfected CHO culture supernates indicating the protein produced is substantially homogeneous (abstract). In addition, observation by the Applicant that the protein of instant invention is glycosylated does not raise to the level of unexpected results because the protein produced in the reference and in the instant invention is structurally and functionally identical.

Furthermore, Applicant also argues that the use of eukaryotic host to produce the protein of interest as opposed to bacterially grown protein to avoid the antigenic effects

of bacterially grown proteins is not a valid ground of motivation to isolate the product of Korn, form it into a composition and use it in the treatment of human diseases. Applicant further asserts that switching to CHO cells will not avoid non-human contaminants.

Applicant also argues that the Office has not provided with any evidence that prior art bacterially produced TNF was known to have problems or that there was any motivation to solve any such problems. This argument has been full considered but is not deemed persuasive. Korn et al. teach that the potential therapeutic applications of TNF would be enhanced by the availability of eukaryotic, endotoxin-free preparations, particularly as the combination of TNF and endotoxin may precipitate septic shock (see page 357, last paragraph). Thus, Korn et. provide the motivation to produce the TNF in eukaryotic cells. Furthermore, Korn et al. also indicate that the previous production of TNF in E.coli cells resulted in low levels of TNF production compared to the production in eukaryotic cells (page 350, 1st paragraph).

Although, Applicant contends that there is no practical consideration that would motivate one of ordinary skill in the art to use the techniques of Allet on the product of Korn et al., the motivation to produce TNF in CHO cells is provided by Korn et al. which teaches that the potential therapeutic applications of TNF would be enhanced by the availability of eukaryotic, endotoxin-free preparations, particularly as the combination of TNF and endotoxin may precipitate septic shock. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods disclosed in Korn et al. to produce and purify the glycosylated TNF protein, obtain compositions and use it in treating human disease as taught by Allet et al. One of

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ordinary skill would have been motivated with reasonable expectation of success to modify the methods of Korn et al. because Allet et al. teach that recombinant TNF can be purified and formulated into compositions for treatment of human diseases (column 6, lines 61-67; column 7, lines 35-43 and column 12, line 4 to column 13, line 5).

Therefore, the instant invention is *prima facie* obvious over Korn et al. (1988) in view of Allet et al. (U.S. Patent No: 5,487,984) and the rejection is maintained.

7. New claim rejection necessitated by Applicants amendments.

New Claim Rejections - 35 USC § 112

8. Claims 1-4 and 7-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8a. Claims 1 and 2 are rejected as being vague and indefinite in the recitation of the term "TNF- α is not labeled with a detectable group ". It is unclear how a substantially homogeneous glycosylated human TNF will also not contain a detectable group, which cannot be labeled. It is well known in the art that the glycosylated proteins can also be labeled (Farmar et al., U. S. Patent No: 5, 126, 442). Claims 3, 4 and 7-12 are rejected insofar as they are dependent on rejected claims 2.

9. No claims are allowable over prior art.

10. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS

A handwritten signature in cursive script, reading "Lorraine Spector". The signature is written in black ink and is positioned above the printed name.

**LORRAINE SPECTOR
PRIMARY EXAMINER**